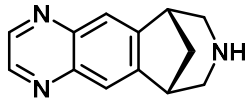
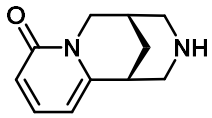
Sarlah Group

Drug of the Week: Varenicline (Chantix)

- Prescription medication for smoking cessation
- Partial agonist of α4β2 nicotinic acetylcholine receptor (nAChR)
- Marketed by Pfizer and approved May 2006
- Major side effects are depression, suicidal thoughts, and nausea
- Derived from the natural product, (–)-cytisine



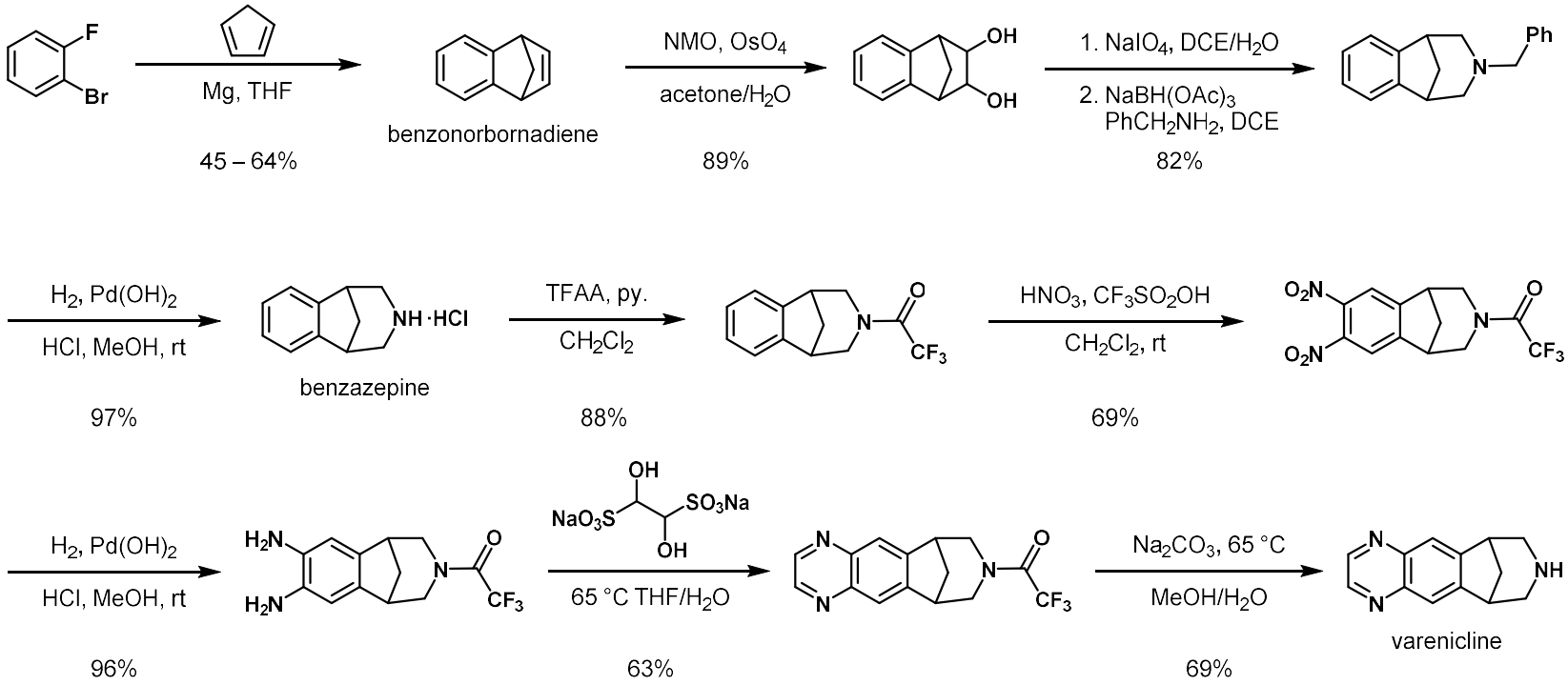
Varenicline



(–)-cytisine

Discovery route: supported developmental efforts through Phase 2 trials

- Utilized a new high yielding route to benzazepine intermediate
- Some considerations for kilo scale-up:
  - Cracking dicyclopentadiene and storing cyclopentadiene
  - Highly reactive benzyne intermediate
  - Osmium contamination



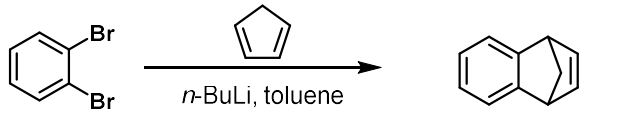
Christopher Bemis, February, 13, 2016

Drug of the Week: Varenicline (Chantix)

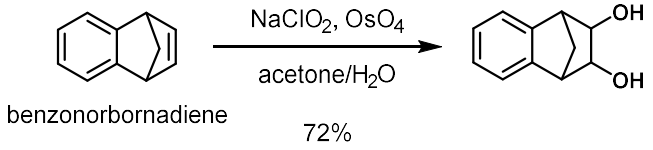
Modifications made to original synthesis for scale-up

- Options for cyclopentadiene storage
  - Dilute with ten volumes of hexanes immediate after cracking and store at –40 °C
  - Store pure cyclopentadiene packed in dry ice at –40 °C to –50 °C

- More efficient benzyne formation for Diels-Alder

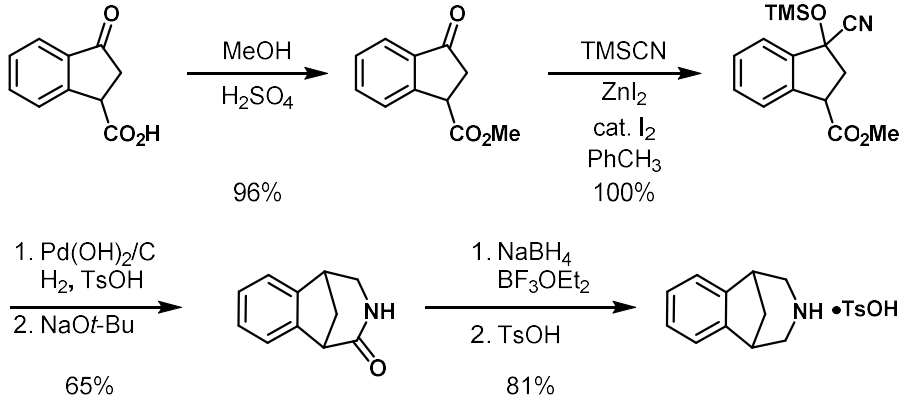
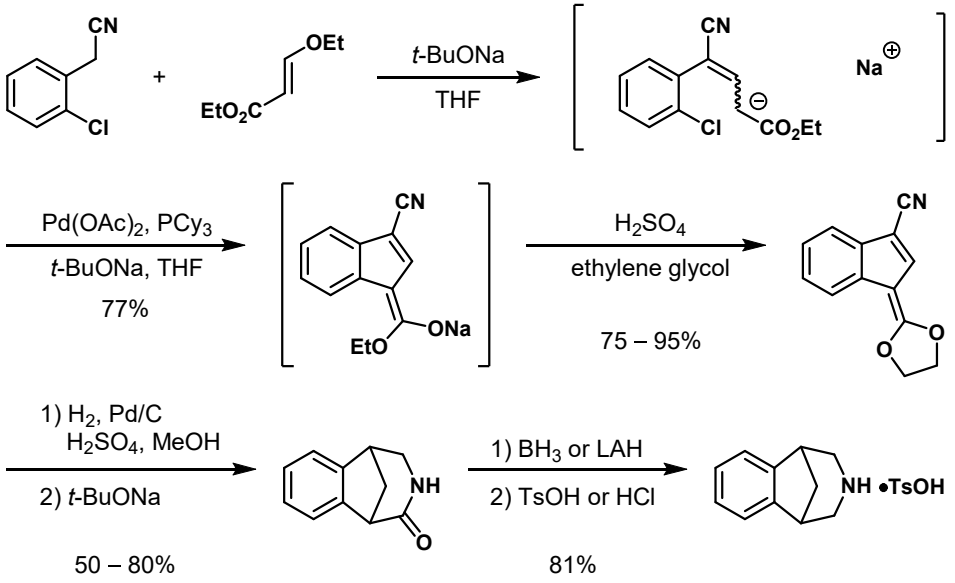


- Lower osmium loadings for dihydroxylation were achieved with an alternative co-oxidant, but in lower overall yields
  - Later discovered that residual osmium was removed in subsequent steps and the NMO usage was continued



- Synthesis of benzazepine needed to be redesigned for a process route after Phase 2 trials due to safety concerns

First successful alternative route to benzazepine:



Final successful alternative route to benzazepine: